Remarks

Claims 1-9, 12, 16-19, and 32-42 are pending in the subject application. By this Amendment, Applicants have canceled claims 1-9, 12, 16-19, 34-37 and 40 and amended claims 32, 33, 38, 39, 41 and 42. Support for the claim amendments can be found throughout the subject specification and in previously presented claims 37-42. Applicants further note that certain of the claims have been amended to revise their dependency in view of the introduction of certain amendments with respect to claims 32-33. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 32-33, 38-39 and 41-42 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants' representatives would like to thank Examiner Chen for the courtesy of the interview conducted on June 17, 2010. The remarks set forth in the Interview Summary Form are consistent with the substance of that interview.

Applicants gratefully acknowledge the Examiner's withdrawal of the objection to claim 1 and the rejections under 35 U.S.C. § 112, second paragraph.

Claims 36, 39 and 42 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Office Action indicates that the phrase "wherein said TCR is human" is vague and renders the claims indefinite. Applicants respectfully assert that the claims as filed are definite and that one skilled in the art would have understood the claims to relate to human TCR. However, in an effort to advance prosecution in this matter, claims 39 and 42 have been amended in a manner that renders this issue moot and claim 36 has been canceled. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 1-9, 12, 16-19, 32, 33 and 34-42 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method for producing a TCR complex wherein the alpha- and beta-chains of an MDM2(81-88)-specific TCR are used as alpha-chain and beta-chain, and wherein the Gly192 of the constant region of the alpha-chain and the Arg208 of the constant region of the beta-chain are exchanged by Arg192 in the constant region of the alpha-chain and by Gly208 in the constant region of the beta-chain, does not reasonably provide enablement for a method in vitro, for producing any other heterodimeric specific wild-type or chimeric TCR having any antigen specificity, wherein glycine, serine, threonine, valine, or alanine is introduced after the

mutagenesis of the DNA molecule that introduces the sterically recessed group including Arg208, and glutamine, glutamic acid, alpha-methylvaline, histidine, hydroxylysine, tryptophan, lysine, arginine, phenylalanine or tyrosine is introduced after the mutagenesis of the DNA molecule that introduces the sterically projecting group including Gly192. Applicants respectfully assert that the claims as filed are enabled.

The Office Action argues that Applicants' last response is not persuasive because the claims read on substituting or mutating various amino acid positions in numerous TCR derived from numerous organisms. With respect to this argumentation, Applicants note that the previously presented claims, such as claims 32, 33 and 37-42, recited amino acid substitutions and mutations that were limited to certain positions (Gly192 in the alpha chain and Arg208 in the beta chain) for human or murine TCR. Thus, it is respectfully submitted that the previously presented, and currently pending claims, are not overly broad and read on limited amino acid substitutions at specific positions within human, murine or humanized murine TCR.

The Office Action further argues that the substitution of various amino acids within the constant regions of a TCR could affect the activity of a TCR. At page 5 of the last Office Action, it is also argued that the teachings of Voss *et al.* do not mean that the claimed substituted or chimeric TCRs would not impair the biological activity of the wild-type TCR and that such substitutions could still affect the biological function and/or specificity of a TCR depending on the type of amino acid being substituted and its position in the TCR constant domain. In this regard, Applicants submit that the evidence of record indicates that amino acid substitutions/mutations at the recited positions do not affect the activity and antigenic specificity of the TCR. As noted previously, evidence regarding the broad applicability of the claimed method has been presented in this matter (see Voss *et al.*, Reference R3 in the Information Disclosure Statement considered by the Examiner on September 19, 2009). In that reference, the authors state (see Abstract):

> We mutated the two residues so as to invert the sense of this interaction analogous to a charged "hole-into-knob" configuration. We show that this inversion in the CαCβ interface promotes selective assembly of the introduced TCR while preserving its specificity and avidity for Ag ligand. Noteworthily, this TCR modification was equally efficient on both a Mu and a Hu TCR. Our data suggest that this approach is generally applicable to TCR independently of their Ag specificity and affinity, subset distribution, and species of origin.

Voss *et al.* not only tested the MDM2 receptor of the invention, but also developed a gp100 receptor. These two receptors show that "the reciprocal mutation approach may be generalized to tumor-reactive TCR with a broad range of Ag affinities" (page 400, right column, second to last paragraph). As also noted above, the claims are limited to amino acid substitutions at the recited positions within murine and human TCR and the evidence of record clearly demonstrates that TCR containing such substitutions/mutations retain antigenic specificity and biological activity (see Voss *et al.*). Furthermore, no evidence of record has been presented by the Patent Office as to how or why one skilled in the art would expect the claimed substitutions/mutations to adversely affect the antigenic specificity and biological activity of a mutated TCR when the evidence of record clearly demonstrates that this is not the case.

Finally, it is noted that the Office Action argues that it is unclear that TCR from different organisms would be amenable to the claimed methods. While Applicants disagree with this assertion, the claims have been amended to indicate that the method is performed on nucleic acids encoding human TCRs, murine TCR or humanized murine TCRs. Thus, it is respectfully submitted that this aspect of the rejection is moot. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested in view of the amendments presented herein and because the evidence or record clearly establishes that the claimed invention is enabled.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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